REMARKS

Status of the Claims

Claims 5 and 25 are pending in the present application. Claims 18, 29, 31, and 32 have been cancelled without prejudice to or disclaimer of the subject matter contained therein. Applicants explicitly reserve the right to file continuing applications directed to the deleted subject matter. Claim 5 has been amended as described elsewhere herein. Support for the amendment may be found in the original claims and specification including, for example, in the background and experimental sections. No new matter has been added by way of amendment. Reconsideration and withdrawal of the rejections are respectfully requested.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 5, 18, 25, 29, and 31-32 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification, while enabling for the treatment of breast, head and neck, gastric, and pancreatic cancer, does not provide an enabling disclosure for the treatment of all cancers. Claims 18, 29, and 31-32 have been cancelled, thereby rendering the rejection of these claims moot. In order to expedite prosecution, claim 5 has been amended to recite that the susceptible cancer to be treated is breast cancer, thereby obviating the rejection. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection Under 35 U.S.C. § 103 Should be Withdrawn

Claims 5, 18, 25, 29, and 31-32 have been rejected under 35 U.S.C. § 103(a) on the grounds that they are obvious in view of WO 99/35146 (Carter *et al.*). Claims 5, 25, and 31-32 have further been rejected under 35 U.S.C. § 103(a) on the grounds that they are obvious over Carter *et al.* in view of U.S. Patent No. 6,268,391 (Dickerson *et al.*). In addition, claims 18, 29, and 31-32 have been rejected under 35 U.S.C. § 103 (a) on the grounds that they are obvious over Carter *et al.* in view of WO 02/24680 (Dean *et al.*). Claims 18, 29, and 31-32 have been cancelled, rendering the rejection of these claims moot. The rejection of claims 5 and 25 is respectfully traversed for the reasons described below.

According to the *MPEP*, three basic criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation to one of skill in the art to combine the references. Second, there must be a reasonable

expectation of success. Finally, the prior art references much teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination, and the reasonable expectation of success must be found in the prior art, and not based on the applicants' disclosure. *MPEP* § 1242, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed Cir. 1991). In addition, when determining whether there was a teaching or suggestion in the prior art to make the claimed combination, the analysis must be explicit. *KSR v. Teleflex*, 127 S. Ct. 1727 (2007).

The references cited in the Office Action do not meet the criteria for establishing a *prima facie* case of obviousness for claims 5 and 25. Claims 5 and 25 are directed to methods of treating a susceptible cancer by administering a compound of formula III and a cRAF-1 inhibitor. Carter *et al.*, Dickerson *et al.*, and Dean *et al.*, either alone or in combination, do not teach or suggest a method of treatment using the particular combination of therapeutic agents recited in claims 5 and 25. Accordingly, no *prima facie* case of obviousness has been established.

Furthermore, even if the cited references did establish a *prima facie* case of obviousness for the subject matter of claims 5 and 25, the inventors have demonstrated that the method of treatment recited in these claims has unexpected results. Specifically, the inventors have shown that combinations of a compound of Formula III and a cRaf-1 inhibitor have enhanced efficacy in inhibiting the growth of a breast cancer cell line. See, for example, Figures 4 and 5 and pages 143-144 of the specification. The inventors have found that the breast cancer cell line HB4a-ras, when treated with a combination of a compound of Formula III and the cRaf-1 inhibitor GW5074, shows vastly increased HB4a-ras cell morality in comparison with the cell mortality seen with either compound alone (see Figure 4). In addition, HB4a-ras cells treated with a combination of a compound of Formula III and the cRaf-1 inhibitor GW5074 show enhanced apoptosis in comparison with either compound alone (see Figure 5). The increased HB4a-ras cell mortality and apoptosis seen for the combination of a compound of Formula III with the cRaf-1 inhibitor BW5074 could not be predicted *a priori* and would not be expected based on the activity of each compound used individually. Thus, the methods recited in claims 5 and 25 recite a therapeutic combination have unexpectedly beneficial results. These results are not taught or suggested by Carter *et al.*, Dickerson *et al.*, and Dean *et al.* alone or in combination. Accordingly, these claims are not obvious in view of the cited references.

In view of the above arguments, all grounds for rejection under 35 U.S.C. §103 have been overcome. Reconsideration and withdrawal of the rejection are respectfully requested.

The Double Patenting Rejection Should be Withdrawn

Claims 5, 18, 25, 29, and 31-32 have been rejected on the ground of nonstatutory obviousness-type double patenting over claims 5-8 of U.S. Patent No. 6,272,256 (the '256 patent). In addition, claims 5, 18, 25, 29, and 31-32 have been rejected on the ground of nonstatutory obviousness-type double patenting over claims 3-6 of U.S. Patent No. 6,713,485 (the '485 patent). Claims 18, 29, and 31-32 have been cancelled, rendering the rejection of these claims moot. The rejection of claims 5 and 25 is respectfully traversed for the reasons described below.

In determining whether a later-filed application is obvious over an earlier filed patent, the test to be applied is whether the invention in a claim in the application is an obvious variation of the invention defined in a claim in the patent. *MPEP* § 804, citing *In re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998). Claims 5-8 of the '256 patent and claims 3-6 of the '485 patent encompass methods of treatment that encompass the administration of a compound of formula (III). However, claim 5 and 25 of the present application are patentably distinct from claims 5-8 of the '256 patent and claims 3-6 of the '485 patent because the claims of the cited patents do not teach or suggest a method of treating breast cancer comprising administering a compound of formula (III) *and* a cRAF-1 inhibitor. As described above, the present application demonstrates that the breast cancer cell line HB4a-ras, when treated with a combination of a compound of Formula III and a cRaf-1 inhibitor, shows vastly increased cell morality in comparison with the cell mortality seen with either compound alone (see Figure 4). In addition, HB4a-ras cells treated with a combination of a compound of Formula III and the cRaf-1 inhibitor GW5074 show enhanced apoptosis in comparison with either compound alone (see Figure 5). The unexpected advantages of this therapeutic combination are not taught or suggested by the claims of the '256 or '485 patent. Accordingly, the claims of the present application are patentably distinct from the claims of the cited patents.

In view of the above arguments, all grounds for the nonstatutory double patenting rejection have been overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

It is believed that the current application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, an interview would expedite prosecution, the Examiner is invited to call the undersigned attorney.

Applicants believe that no fees are due in connection with the filing of this paper other than those specifically authorized herein. However, should any other fees be deemed necessary to effect the timely filing of this paper the Commissioner is hereby authorized to charge such fees to Deposit Account No. 07-1392.

Respectfully submitted,

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